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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/501,028	03/14/2005	Christopher M. Starr	15021-6	1759

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EXAMINER	
SRIVASTAVA, KAILASH C	
ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,028	STARR ET AL.	
	Examiner	Art Unit	
	Dr. Kailash C. Srivastava	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9 and 11-29* is/are pending in the application.

4a) Of the above claim(s) *6,15 and 21-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,7-9,11-14 and 16-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicants' response and amendments filed 24 April 2008 to Office Action mailed 29 January 2008 is acknowledged and entered.

Informal Matters

2. Applicants' confirmation of election of Group I invention comprising Claims 1-20 in the response cited supra is appreciated and made of record. Applicants, however, have not confirmed the election of species of:

(i) Sandhoff disease; and

(ii) protein, β-hexosaminidase A

according to the response filed 09 November 2007 (See, Page 2, Lines 12-13).

3. For the record, contrary to the assertion made in the response filed 24 April 2008 (See, Remarks/Arguments numbered Page 8 at the bottom of said Page, Lines 18-21), Examiner withdrew Claims 6, 15 and 21-29 and additional species recited in Claims 12-13 and 20 because of the Election of invention and elected species of protein, β-hexosaminidase A whose deficiency causes the lysosomal storage disease according to Claim 1 from which Claims 6, 12-13, 15 and 20 depend (See Office Action mailed 29 January 2008, Page 2, item 4, Line 21). Note further that applicants elected on record the species of protein, β-hexosaminidase A whose deficiency causes the lysosomal storage disease.

4. For the record, also note, contrary to the assertion made in the response filed 24 April 2008 to the Office Action mailed 29 January 2008:

- Examiner, rather than objecting (See, Remarks/Arguments numbered Page 8 at the bottom of said Page, Line 30), rejected Claims 14-20 under non-statutory obviousness-type Double Patenting;

- Examiner, rather than objecting (See, Remarks/Arguments numbered Page 9 at the bottom of said Page, Lines 14-19), rejected Claim 10 under 35 U.S.C. §112, second paragraph; and

- Examiner, rather than objecting (See, Remarks/Arguments numbered Page 9 at the bottom of said Page, Lines 20-22), rejected Claims 1-5, 7-14 and 16-20 under 35 U.S.C. § 103(a) as obvious over the combined teachings from Neuwelt (US Patent 4,866,042) in view of Wikimedia Foundation, Inc., (See Sandhoff disease,

http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008) and Jeffries et al (US Patent 5,981,194) and further in view of LeBowitz (USPGPB 2003/0072761 A1).

Please note, as the applicant may also be well aware, rejections and objections have different weight in regards to an Office Action.

Withdrawals of Objections/Rejections

5. In view of applicants' remarks and amendment filed 24 April 2008, following objections/rejections in the Office Action mailed 29 January 2008 are hereby withdrawn:

- Objection to specification for lack of application priority data on the first page of the specification;
- Objection to Claim 10;
- Double patenting rejection to Claims 14-20 over Claims 1-2 of the co-pending U.S. Non-Provisional application Number 10/588, 425;
- Indefiniteness rejection to Claim 10 under 35 U.S.C. §112, second paragraph; and
- obviousness rejection to Claims 1-5, 7-14 and 16-20 under 35 U.S.C. §103(a) as obvious over the combined teachings from Neuwelt (US Patent 4,866,042) in view of Wikimedia Foundation, Inc., (See Sandhoff disease, http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008) and Jeffries et al (US Patent 5,981,194) and further in view of LeBowitz (USPGPB 2003/0072761 A1).

Claims Status

6. Claim 10 is currently cancelled.

7. Claims 1-9 and 11-29 are currently pending.

8. Claims 21-29 remain withdrawn.

9. Claim 1 has currently been amended.

10. Examiner has previously withdrawn Claims 6, 15 and all other Markush Group species listed in Claims 12-13 and 20, except for the applicants' elected:

Sandhoff disease in Claim 12; and

β-hexosaminidase A as the protein in Claim 13 and 20.

11. Claims 1-5, 7-9, 11, Sandhoff disease in Claim 12, β-hexosaminidase A as the protein Claimed in Claim 13, Claims 14, 16-19 and β-hexosaminidase A as the claimed protein in Claim 20 are examined on merits.

12. Note, Claims 6 and 15 were withdrawn in the Office Action mailed 29 January 2008. However, in the identifiers for the Claims 6 and 15 in the amendment filed 24 April 2004, Claims 6 and 15 have been identified as "Original". Accordingly, Claims 6 and 15 do not conform to the proper identifiers under 37. CFR §1.121 (See, M.P.E.P. §714 [R-5] c).

In the interest of advancing the prosecution, however, the Examiner is further Examining the Claims as identified in item 11 *supra*.

Claim Rejections - 35 U.S.C. §103

13. The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> ***A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.***

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §102(f) or (g) prior art under 35 U.S.C. §103(a).

15. Claims 1-5, 7-14 and 16-20 are rejected under 35 U.S.C. §103(a) as obvious over the combined teachings from Zankel et al. (US 20050026823 A1) in view of Wikepedia (Wikimedia Foundation, Inc., http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008) and Jeffries et al (US

Patent 5,981,194) and further in view of Neuwelt (US Patent 4,866,042) and LeBowitz (USPGPB 2003/0072761 A1).

Claims are drawn to a method and a composition, wherein a composition, i.e., a conjugate, comprising soluble human p97 covalently linked to a protein by a linker of 5-20 carbon atoms is intravenously administered to a subject in need thereof to treat a lysosomal storage disease. Said conjugate passes through the blood brain barrier (i.e., BBB). In said composition, the lysosomal storage disease is Sandhoff disease and the protein is β-hexosaminidase A.

Zankel et al., teach, "The blood-brain barrier (BBB) significantly impedes access of therapeutic agents by the inability of therapeutic enzymes to gain access to brain cell lysosomes and teach compounds of conjugates of therapeutic or active agents with a polypeptide, pharmaceutical compositions thereof and methods for using said compositions to treat lysosomal storage diseases (i.e., LSDs; See, Abstract, Lines 1-7; Paragraph 0004, Lines 1-15). According to Zankel et al., intravenous enzyme replacement therapy (ERT) is beneficial for LSDs". Accordingly, a method of delivering the replacement enzyme across the BBB and into the lysosomes of the affected cells would be highly desirable (Paragraph 0004, Lines 1-15). Furthermore, the lipoprotein receptor-related protein (i.e., LRP, e.g., the chaperone receptor-associated protein (i.e., RAP), selectively bind to LRP receptors and, as carriers or vectors, RAP serves to increase the transport of therapeutic agents across the BBB and/or deliver agents to lysosomes of cells within and without the central nervous system (i.e., CNS (Paragraph 0012, Lines 2-6). Zankel et al., also teach compounds comprising RAP or a RAP polypeptide conjugated to a therapeutic agent and pharmaceutical compositions thereof, a bioactive protein or peptide covalently linked to the RAP joined by linker groups and PEGylation of the RAP moiety of the conjugate, wherein said active agent is a human enzyme and the compound is a fusion protein of RAP and an active agent protein or polypeptide portion. The agent, polypeptide portion of the fusion protein may be a substance having therapeutic (Paragraph 0013, Lines, 1-23). Zankel et al., also teach a method to treat a lysosomal storage diseases (e.g., Tay-Sachs disease), wherein a lysosomal protein deficiency contributes to said disease state by administering RAP or a RAP polypeptide conjugated to a therapeutic agent , or RAP fused with a therapeutic enzyme, wherein the RAP-enzyme complex binds to an LRP receptor and is transported across the cell membrane, enters the cell and is delivered to the lysosomes within the cell. (Paragraph 0025, Lines 1-17). Please note, Toy-Sach's Disease and Sandhoff disease are GM2 gangliosidoses (Sandhoff disease, Tay-Sachs disease) related diseases caused by the deficiency of β-hexosaminidase A (See Sandhoff disease, Wikimedia Foundation, Inc., http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008). Zankel et al., however, do not elaborate that the material administered is a soluble p97 molecule, or a

linking group is 4-20 atom length.

LeBowitz teaches Tray-Sachs Disease is caused by deficiency in β-hexosaminidase A and teaches compositions comprising and delivering therapeutic agents and fusion proteins comprising said material to overcome enzymatic defects associated with lysosomal storage disease (Table 1, Line10; Page 5, Column 2, Paragraphs 0057-0058; Paragraphs 0062-0063; Example 5). Please note, Toy-Sach's Disease and Sandhoff disease are GM2 gangliosidoses (Sandhoff disease, Tay-Sachs disease) related diseases caused by the deficiency of β-hexosaminidase A (See Sandhoff disease, Wikimedia Foundation, Inc., http://en.wikipedia.org/wiki/Sandhoff_disease, Modified 2007; Printed 1/16/2008).

Jeffries et al. teach a composition comprising p97 for delivering an agent across the BBB in association with a pharmaceutical carrier, wherein p97 is conjugated to the substance to be delivered in a pharmaceutical composition (Column 8, Lines 54-67) and also teach delivering said composition to the subject in need thereof to treat a lysosomal storage disease (Column 101, Line 25 to Column 102, Line 2).

Neuwelt teaches, lysosomal storage diseases are the result of blood brain barrier (i.e., BBB) and a method to treat said diseases through delivering/incorporating directly into the human/subject brain tissue in need thereof, the corrective compound comprising the lacking moiety (e.g., a ligand, an enzyme or enzyme substrate). Said material is injected intravenously or intra-arterially, followed by injecting a hyper-osmotic solution of a compound (e.g., mannitol) that temporarily disrupts the BBB (Column 9, Line 30 to Column 10, Line 28; Column 13, Line 25 to Column 14, Line 13). Said material is a pharmaceutical composition comprisimg a linker that is complimentary to both the vector and the inserted material (Column 8, Lines 29-68; Column 14, Lines 1-30). Prior to injecting said composition in the subject in need thereof, said preparation is screened for therapeutic activity to pass through the BBB via labeling the vector with radioactive sulfur (i.e., ^{35}S). Subsequently a pharmaceutical composition comprising non-labeled (i.e., without 35S) said preparation is injected to the subject in need thereof. Thus, Neuwelt teaches treating a lysosomal storage disease (e.g., Toy- Sach's) via administering a pharmaceutical composition comprising a protein covalently conjugated to a material whose deficiency causes said disease. The atom chain length for said linker is intrinsically the same as claimed because the prior art teaches a composition comprising same ingredients and steps as claimed instantly.

One having ordinary skill in the art at the time of claimed invention would have been motivated to combine the teachings from Zankel et al., with the beneficial teachings from LeBowitz, Jeffries et al., and Neuwelt; because LeBowitz teaches that Tay-Sach's Disease is because of the absence or defect in

the presence of β-hexosaminidase A and is corrected by administering to an individual in need of a composition comprising β-hexosaminidase A that is a fusion protein, Jeffries et al. expressly define a composition comprising p97 to be delivered to a subject in need of said pharmaceutical composition in treating lysosomal storage disease and Newlet teaches treating a lysosomal storage disease (e.g., Toy-Sach's) via administering a pharmaceutical composition comprising a protein covalently conjugated to a material whose deficiency causes said disease. The atom chain length for said linker is within the same range of atom chain length as claimed. The actual concentrations of individual components for preparation of said pharmaceutical composition may not be the same as instantly claimed. However, the adjustment of particular conventional working components/ conditions (e.g., types of complimentary materials having same physiological effects and concentrations thereof) is deemed merely a matter of judicious selection and routine optimization of a result-effective parameter, which is well within the purview of the skilled artisan. In view of the fact that the applicant's invention also recites composition comprising same components, and methods comprising the same steps and ingredients as are disclosed in prior art teachings; applicant's invention is obvious over the teachings of Examiner-cited prior art references.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify/combine the teachings from Zankel et al., with the beneficial teachings from LeBowitz, Jeffries et al., and Neuwelt; because all of the prior art references teach treating a composition and administering said composition to treat a lysosomal storage disease. LeBowitz teaches that Tay-Sach's Disease is because of the absence or defect in the presence of β-hexosaminidase A and is corrected by administering to an individual in need of a composition comprising β-hexosaminidase A that is a fusion protein, while Jeffries et al. remedy the deficiency in Zankel et al's teachings of expressly defining a composition comprising p97 to be delivered to a subject in need of said pharmaceutical composition in treating lysosomal storage disease and Newlet teaches treating a lysosomal storage disease (e.g., Toy- Sach's) via administering a pharmaceutical composition comprising a protein covalently conjugated to a material whose deficiency causes said disease. The atom chain length for said linker is within the same range of atom chain length as claimed. It is also *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." (*In re Kerkhoven*, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted)).

From the teachings of the references cited *supra*, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

16. Applicants ' amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. §706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. §1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

17. For the aforementioned reasons, no claims are allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Kailash C. Srivastava whose telephone number is (571) 272-0923. The examiner can normally be reached on Monday to Thursday from 7:30 A.M. to 6:00 P.M. (Eastern Standard or Daylight Savings Time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Jon Weber can be reached at (571)-272-0925 Monday through Thursday 7:30 A.M. to 6:00 P.M. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding may be obtained from the Patent Application Information Retrieval (i.e., PAIR) system. Status information for the published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (i.e., EBC) at: (866)-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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27 July 2008

David M. Naff/
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